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Effect of continuous positive airway pressure on insulin growth factor-1 in patients with obstructive sleep apnea: A meta-analysis

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ABSTRACT

Objective: Obstructive sleep apnea (OSA) has been recognized as being associated with low level of insulin growth factor-1 (IGF-1). However, the impact of OSA treatment using continuous positive airway pressure (CPAP) on IGF-1 remains controversial. We performed a meta-analysis to determine whether effective CPAP therapy could increase IGF-1 levels.

Design: Two reviewers independently searched PubMed, Cochrane library, Embase and Web of Science before September 2014. Information on characteristics of subjects, study design and pre- and post-CPAP treatment of serum IGF-1 was extracted for analysis. Standardized mean difference (SMD) was used to analyze the summary estimates for CPAP therapy.

Results: Six articles with 168 patients were included in this meta-analysis, including five observational studies and one randomized controlled study. The meta-analysis showed that CPAP was associated with a statistically significant increase in IGF-1 in OSA patients (SMD = −0.436, 95% confidence interval = −0.653 to −0.218, $P = 0.000$).

Conclusions: This meta-analysis suggested that CPAP therapy was associated with an increase in IGF-1 in patients with OSA. Further large-scale, well-designed interventional investigations are needed to clarify this issue.

1. Introduction

Obstructive sleep apnea (OSA) is a common medical condition characterized by repetitive partial or complete obstruction of the upper airway [1]. The prevalence of OSA is estimated to be 2% to 4% in the general population and 35% to 45% in obese individuals [2,3]. The repetitive episodes of upper-airway obstruction in sleep apnea are often associated with repetitive nocturnal oxygen desaturation and arousals that disrupt sleep architecture and reduce slow-wave sleep, both of which could affect the sleep-entrained or diurnal rhythms of pituitary-dependent hormones [4].

Insulin growth factor-1 (IGF-1) is a 7.7-kDa single-chain polypeptide of 70 amino acids that is similar in sequence to proinsulin [5]. Growth hormone (GH) stimulates the synthesis of IGF-1 in the liver and regulates the paracrine production of IGF-1 in many other tissues. IGF-1 is considered to be an important growth factor, mediating the anabolic and linear growth promoting effect of pituitary GH protein [6]. An accumulating body of evidence showed that OSA was associated with significant decrease in serum IGF-1 [7–9].

An effective noninvasive treatment for OSA has become available and continuous positive airway pressure (CPAP) may eliminate hypoxic episodes and result in improved sleep. However, a number of studies [8,10–15] have yielded conflicting results regarding the impact of CPAP therapy on IGF-1 levels in OSA patients, among those most studies with small sample size, which have not enough statistical power to address this issue adequately and effectively. In this study, a meta-analysis was conducted to quantitatively evaluate the impact of CPAP on IGF-1 levels in OSA patients.

2. Methods

2.1. Search strategy

We searched PubMed, Web of Science, Cochrane Library and Embase before September 2, 2014, on original English language studies, using the following search terms(continuous positive airway pressure or CPAP) and (sleep apnea or sleep apnoea) combined with (insulin growth factor-1 or IGF-1 or somatomedin C). In addition, the reference lists of relevant publications were manually searched for related studies. Two independent assessors identified relevant studies based on title and abstract that included empirical data related to the treatment effect on IGF-1 in OSA.

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2.2. Inclusion/exclusion criteria of literature

Studies were included if they met the following criteria: (1) All subjects of the study were limited to adults(age > 18) with newly diagnosed OSA. (2) The intervention was an application of CPAP. (3) The study must have both before and after CPAP IGF-1 values reported. (4) CPAP had to be used for ≥ 4 weeks before and after repeat IGF-1. (5) The study provided sufficient data that allowed for a meta-analysis. When multiple studies reported outcomes using the same patient group, the study with the largest population was included.

Excluded criteria were as follows: (1) studies that did not satisfy the inclusion criteria would be excluded; (2)non-English article; (3) abstracts, case reports, editorials, expert opinions, letters, animal studies and reviews without original data; and (4)unpublished data from conference. If the required data of studies was ambiguous, the corresponding author was contacted; after two no-response attempts, the studies were also ruled out. Any disagreement between the two reviewers was resolved by discussing with a third reviewer.

2.3. Data extraction

Data were extracted from each study by a single author and then reviewed by a second author to ensure that no errors were made. The following variables were extracted from each study: first author, publication year, country of the study, sample size, patient inclusion criteria, participant characteristics, study design, mean daily CPAP usage time, duration of CPAP therapy, serum IGF-1 levels before and after CPAP treatment.

2.4. Statistical analysis

The meta-analysis was conducted using Stata statistical software(Version 12.0, Stata Corporation). Considering IGF-1 measured and reported differently, standardized mean difference (SMD) was used for analyzing the summary estimates. Q and I^2 statistics were used to determine statistical heterogeneity among individual studies [16]. Heterogeneity was considered to be significant at $p < 0.10$ for the Q statistic [17]. An I^2 greater than 50% was considered substantial heterogeneity in this meta-analysis. Random-effects model was performed to combine effect size if significant heterogeneity was observed; otherwise, fix effects model was conducted. Sensitivity analysis was conducted to investigate the influence of a single study on overall efficacy of CPAP. Publication bias was presented using funnel plot and tested by "Begg test" and "Egger test." A $p < 0.05$ was adopted as statistical significance.

3. Results

3.1. Searching results

A total of 39 studies were retrieved to screen after searching duplication. After review of the titles and abstracts, 27 studies were excluded whereas 12 were considered to be potentially relevant. Of the 12 studies, 6 were excluded from the sample for the following reasons: 1 was conference article [18], 2 lacked essential data [19,20], the data of one study presented as bar graph [21], one study had no measure unit of essential data [22] and one study in which therapy duration <4 weeks [23]. The detailed steps of the literature search were shown in Fig. 1.

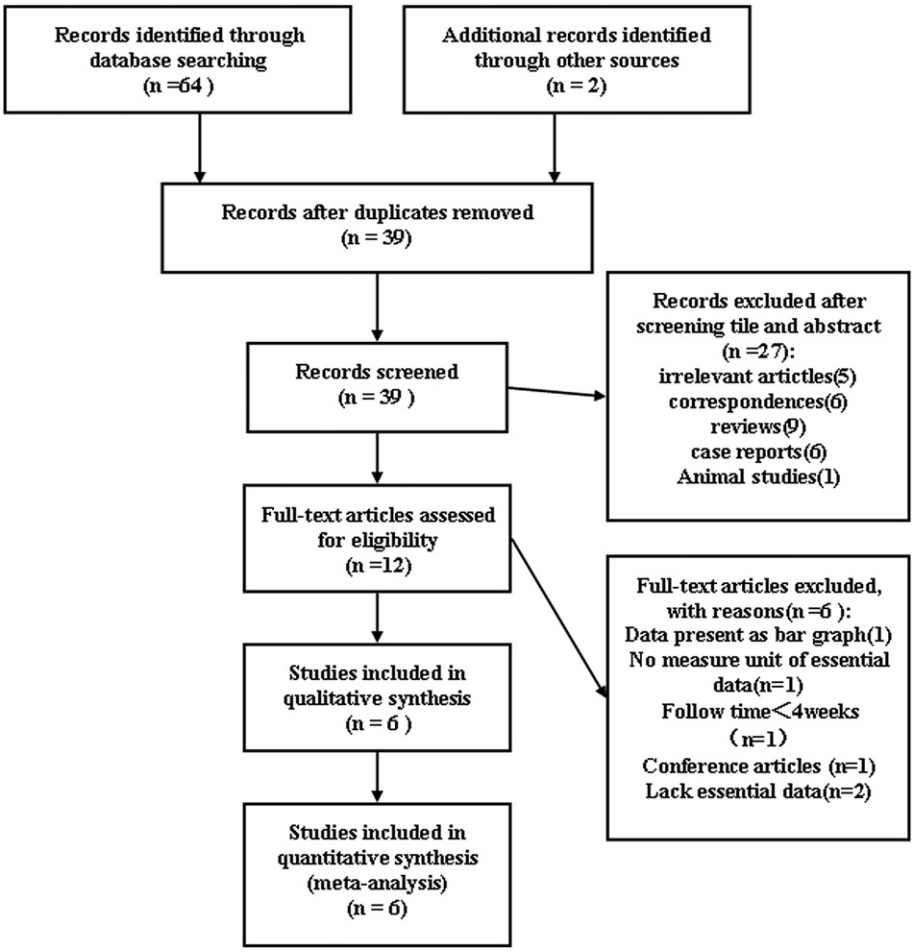

Fig. 1. Flow diagram of study selection.

Table 1
Characteristics of include studies.

Study	Year	Nation	Sample size/male	Inclusion criteria	Ventilation duration/night (h)	Therapy duration (M)	Study design
Grunstein	1989	Australia	43/43	ODI > 30	NR	3	Observational study
Brooks	1994	Australia	9/7	Moderate and severe OSA	NR	4	Observational study
Meston	2003	UK	52/52	ODI ≥ 10	5.4 ± 1.6	1	RCT
Lindberg	2006	Sweden	11/11	AHI ≥ 10	5.7 ± 1.9	6	Observational study
Barcelo, EDS	2008	Spain	20/20	OSA	5.5 ± 1.3	3	Observational study
Barcelo, non-EDS	2008	Spain	15/15	OSA	5.7 ± 1.3	3	Observational study
Makino	2012	Japan	18/18	AHI ≥ 40	>4 h	17.5	Observational study

Abbreviation: ODI = oxygen desaturation index, OSA = obstructive sleep apnea, RCT = randomized controlled trial, AHI = apnea–hypopnea index, EDS = excessive daytime sleepiness, NR = not reported.

3.2. Characteristics of the included studies

A total of 6 articles that included 7 cohorts involved 168 patients met the inclusion criteria and were included in this meta-analysis. One of them was randomized clinical trial (RCT) [10], 5 were observational studies [8,13,14,24,25]. One study [12] reported results separately for the 3-week group and the 6-month group, and only the data of the 6-month group was extracted. Another study [14] reported all results separately for OSA group without excessive daytime sleepiness (EDS) and OSA with EDS group. Four studies [13,14,24,25] defined OSA based on apnea–hypopnea index (AHI), while the other two studies [8,10] defined OSA based on oxygen desaturation index (ODI). The information of author, year of publication, nation, sample size, inclusion criteria, mean daily CPAP usage time, therapy duration and study design of each study were shown in Table 1. The information of mean age, body mass index (BMI), AHI, lowest O_2 saturation ($LowSO_2$) and IGF-1 of each study were summarized in Table 2.

3.3. Pool analysis

The heterogeneity test showed that there were no significant differences across individual studies (chi-squared = 3.87, $p = 0.695$; $I^2 = 0.0\%$).Therefore, a fixed-effects model was used for the pooled analysis. Pooling the data with a meta-analysis showed that CPAP was associated with a statistically significant increase in IGF-1 in OSA patients (SMD = −0.436, 95% confidence interval (CI) = −0.653 to −0.218, $z = 3.93$, $p = 0.000$) (Fig. 2).

3.4. Sensitivity analysis and publication bias

Sensitivity analysis demonstrated that omitting any one of the studies at a time did not influence the results, confirming non-robust overall results. The funnel plot (Fig. 3) showed that small publication bias seemed to exist. However, Begg's tests ($p = 0.368$) and Egger's tests ($p = 0.507$) showed there was no evidence to support publication bias in our study.

4. Discussion

This meta-analysis including 6 studies and 7 cohorts quantitatively evaluated the efficacy of CPAP on IGF-1 in patients with OSA. The results of this meta-analysis indicated that CPAP was associated with a statistically significant increase in IGF-1 in OSA patients (SMD = −0.436, 95% CI = −0.653 to −0.218, $z = 3.93$, $p = 0.000$).

To our best knowledge, present study was the first meta-analysis addressing the effect of CPAP on IGF-1. Our meta-analysis has several strengths. First, pooling of the interesting data from all eligible studies yielded more precise and reliable conclusions than the data from individual study. Second, Begg tests ($p = 0.368$) and Egger's tests ($p = 0.507$) showed there was no evidence to support publication bias in our study. Third, $I^2 = 0.0\%$ ($I^2 < 50\ \%$) and $p = 0.695$ ($p > 0.1$), indicating that there existed no heterogeneity among the studies. Therefore, the six studies were comparable and homogeneous, and the results of our study could represent the true relationship between CPAP therapy and plasma IGF-1 levels.

The association between OSA and IGF-1 has been suggested by several studies [7–9]. In a cross-sectional analysis of 77 male consecutive patients suspected for OSA, Ursavas et al. [7] demonstrated that there was a significant negative correlation between IGF-1 and OSA severity regardless of BMI. Another study also found that IGF-1 was significantly lower in relation to the severity of sleep apnea independent of age and obesity [8]. Sleep fragmentation, repetitive hypoxia induced by OSA, may be the mechanism linked the association. GH secretion occurs mostly during sleep, and 70% of nocturnal GH pulses are associated with slow-wave sleep [26]. In OSA patients, GH and IGF-1 secretion are decreased due to reduction in the amount of slow-wave sleep induced by sleep fragmentation. Experimental evidence from animal studies supports that hypoxia inhibits GH release or biosynthesis [27]. Hyperoxia increases the expression of IGF-1 and its type I receptors in mice model [28]. CPAP is the most efficient therapy for maintaining upper-airway patency during sleep. CPAP treatment improves sleep architecture and oxygen saturation [29], and these factors contribute to the low levels of IGF-1 in OSA patients. Therefore, it is not unexpected that CPAP therapy could increase IGF-1 levels in OSA patients.

Table 2
Patients' characteristics of the trials included in the meta-analysis.

Study	Age	BMI	AHI or ODI	$LowSO_2$	Pre-CPAP, IGF-1	Post-CPAP, IGF-1
Grunstein	NR	NR	NR	NR	580 ± 262 U/L	770 ± 262 U/L
Brooks	50.8 ± 9.6	42.7 ± 4.3	47 ± 31.6	74 ± 9.5	13.9 ± 4.8 nmol/L	13.6 ± 3.8 nmol/L
Meston	50 (33–71)[b]	35.1 (25.8–44.3)[b]	32.9 (15.5–63.4)[a,b]	NR	10.50 ± 3.23 nmol/L	11.59 ± 3.48 nmol/L
Lindberg	67 ± 7	28.3 ± 4.3	27 ± 12	75 ± 10	116 ± 32 ng/ml	138 ± 56 ng/ml
Barcelo, EDS	49 ± 6	32 ± 3	52 ± 19	69 ± 12	122 ± 99 ng/ml	145 ± 134 ng/ml
Barcelo, non-EDS	50 ± 5	31 ± 4	48 ± 16	81 ± 8	113 ± 25 ng/ml	127 ± 28 ng/ml
Makino	35.9 ± 3.0	28.7 ± 5.1	52.3 ± 27.6	75.9 ± 15.3	153.1 ± 25.5 ng/ml	170.5 ± 39.5 ng/ml

Abbreviation: BMI = body mass Index, AHI = apnea–hypopnea index, ODI = oxygen desaturation index, $LowSO_2$ = lowest O_2 saturation, CPAP = continuous positive airway pressure, IGF-1 = insulin growth factor-1, NR = not reported, EDS = excessive daytime sleepiness.
[a] Presented as oxygen desaturation index (ODI).
[b] Presented as median (5th–95th centiles).

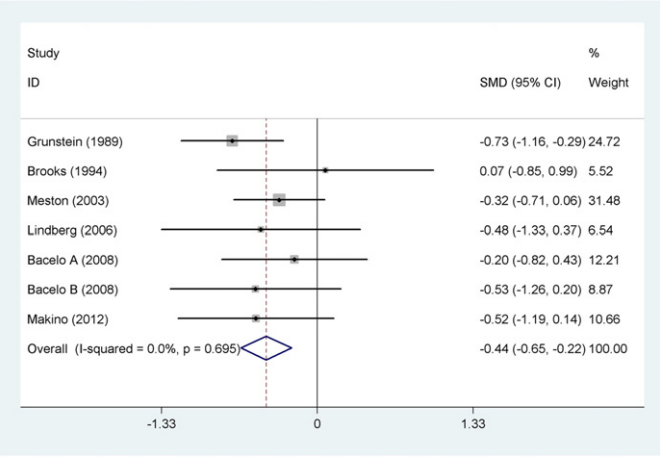

Fig. 2. Meta-analysis and forest plot of all studies included. Calculations based on a fixed-effects model. Abbreviation: SMD = standardized mean difference.

A growing body of evidence from clinical research supported the relationships of OSA with increased cardiovascular complications, and as a noninvasive treatment of OSA, CPAP can significantly reduce cardiovascular morbidity and mortality [30,31]. The underlying mechanisms mediating these associations might include sympathetic nervous system activation and systemic endothelial dysfunction [32]. However, low levels of IGF-1 may also contribute to an increased risk of cardiovascular disease in OSA patients. Some investigations reported that low IGF-1 was tightly associated with increased risk of coronary artery disease [33,34]. A large prospective study showed that initially healthy subjects in the low IGF-1 quartile had an adjusted relative risk of 1.94 (95% CI = 1.03 to 3.66) for ischemic heart diseases compared with controls during the 15-year follow-up period [33]. A cross-sectional study covering 218 healthy subjects found that high fasting serum free IGF-1 levels were associated with decreased presence of atherosclerotic plaques and coronary artery disease [34]. Our meta-analysis suggested that CPAP treatment appeared to significantly increase IGF-1 levels in OSA patients, and we speculated that it might be beneficial to delay or prevent the occurrence of cardiovascular disease in patients with OSA.

In contrast to our report, the only RCT showed that CPAP treatment has no beneficial effect on IGF-1 when compared to a sham treatment. The reasons for this similar improvement in both groups are not clear but may be due to the increased physical activity, as evidenced by the increased energy and vitality dimension of the SF-36 scores. Akerstedt et al. [35] studied 12 healthy males who were exposed to 48 hours of sleep deprivation and concluded that sleep deprivation resulted in lower levels of both psychological and physical activity. Exercise has been shown to directly stimulate GH secretion and elevation of activity levels may therefore lead to the return of physiological GH release [36].

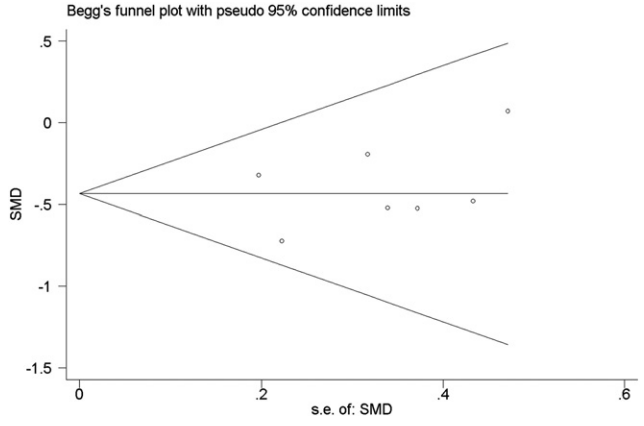

Fig. 3. Funnel plots for assessing publication bias of studies included. Abbreviation: SE = standard error, SMD = standardized mean difference.

Several limitations of our study have to mention. First, the number and size of studies included in this analysis was relatively small and larger and more studies would allow for more precise effect size estimation. Second, most of the included studies were self control, not RCT. Performing an RCT would be unethical because patients with confirmed OSA would have to be left untreated to monitor the potential changes in IGF-1 levels. There was only one RCT that examined the effects of CPAP therapy on IGF-1 levels but unexpectedly failed to identify increase in IGF-1 levels with CPAP therapy compared to sham therapy. Third, almost all of the study subjects were male; therefore, the results may not be generalizable to female patients. It is also a limitation of our meta-analysis that we were unable to include the data from the study by Munzer et al. [15] because an increase in IGF-1 levels with CPAP in a subset of men but not in women was reported. Fourth, in most of the studies, the primary outcome assessment did not consider the effect of CPAP therapy on IGF-1 levels, which increased the risk of a selection bias. Fifth, in our meta-analysis, different studies utilized a variety of measurement techniques for IGF-1, ranging from enzyme immunoassay [10], chemiluminescent detection [14], radioimmunoassay [8,13] and immunoradiometric assay [24]. Considering IGF-1 measured and reported differently, SMD was used for analyzing the summary estimates instead of the absolute levels of IGF-1. In addition, the GH/IGF-1 axis consists of GH, IGF-1, insulin-like growth factor binding protein (IGFBP) and acid-labile subunit (ALS). The present study only addressed the effect of CPAP therapy on IGF-1. It may, to some extent, weaken the impact of the work. Finally, only papers published in English were enrolled, it may cause potential publication bias.

In conclusion, our meta-analysis suggested that CPAP among OSA patients was significantly associated with an increase in IGF-1. However, the interpretation of the pooled results should be cautious because of the low quality of evidence, and further prospective large-scale multicentre RCTs are needed to explore the precise impact of CPAP therapy on IGF-1 and other elements of GH/IGF-1 axis.

Conflict of interest

The authors declare that they have no conflict of interest.

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